REMARKS

In this Amendment, Applicant has cancelled Claims 29 – 42 and 44 – 45 without prejudice or disclaimer, and amended Claims 1 – 28. Claims 1, 4, 6, 19 – 21, 24, 25 and 28 have been amended to specify various embodiments of the present invention and overcome the rejection. Claims 2, 3, 5, 8 – 18, 22, 23, 26 and 27 have been amended to proper dependent form, or rephrase certain expressions or correct clerical errors. In addition, the specification has been amended to rephrase certain expressions and correct clerical errors. The amendment is editorial in nature. It is respectfully submitted that no new matter has been introduced by the amended claims and specification. All claims are now present for examination and favorable reconsideration is respectfully requested in view of the preceding amendments and the following comments.

INFORMATION DISCLOSURE STATEMENT:

The Examiner indicated that certain references listed in the PTO 1449 form of the Information Disclosure Statement filed on May 2, 2002 were missing. Applicant hereby respectfully resubmits the missing references indicated by the Examiner in a concurrently filed Information Disclosure Statement for consideration. Proper fees have been enclosed regarding the submission of the Information Disclosure Statement.

OBJECTION TO SPECIFICATION:

The specification has been objected as containing informality.

It is respectfully submitted that the informalities contained in the specification have been corrected as follows:

In page 4, line 24, "SEQ ID NO: 1" has been inserted after "KLVFF." The same change has been made throughout the specification.

In page 4, line 34, "SEQ ID NO:5" has been inserted after "KKLVFFA"; please note that this sequence is different from the sequence identified as SEQ ID NO:3. A new sequence listing in both paper form and computer readable form has been hereby submitted to include the SEQ ID NO:5;

In page 9, line 30, it is respectfully submitted that the Examiner's suggestions are incorrect. In the specification, "R" groups have not been included in the formula of the proposed peptide back-bone replacement groups, because these peptide back-bone replacement groups would not then be able to replace the CONH groups within the peptide backbone. For example, the nitrogen atom in CONH forms three bonds (two with the neighboring carbon atoms in the peptide backbone and one with the hydrogen atom), but the oxygen atom in COO only forms two bonds (one with each of the neighboring carbon atoms in the peptide backbone). Therefore, COOR would be incorrect, because such a group would not be able to replace the CONH group by forming a bond with each of the two neighboring carbon atoms in the peptide backbone. In addition, "(thioester)" has been added after "COS" and "(dithioester)" has been added after CSS.

In page 16, lines 35, "monomers are amino-acids" is changes to "amino acid residues" according to Examiner's suggestion. The same change has been made throughout the specification.

In page 22, lines 19, "SEQ. ID. NO. 1" is changes to "SEQ ID NO:1" according to Examiner's suggestion. The same change has been made throughout the specification for this and other sequence listings.

In addition, "α-L-amino-acids" is changed to "α-L-amino acid" throughout the specification.

Therefore, objection to the specification is overcome and withdrawal of the objection is respectfully requested.

OBJECTION TO CLAIMS:

Claims 1, 8, 16, 17, 21 and 26 have been objected as containing informality.

It is respectfully submitted that the objection has been overcome by the presently submitted amendments.

In Claim 1, "α-L-amino-acids" is changed to "α-L-amino acid."

In Claim 8, it is respectfully submitted that the term "β-sheet propensity" should NOT be changed to "β-structure propensity", because "β-sheet propensity" is the technical term that is used in many biochemistry textbooks and is more familiar to those skilled in the art. In addition, "β-sheet propensity" is clearly defined on page 18 of the specification and at no stage does Applicant use the term "β-structure propensity".

In Claims 16 – 17, "SEQ ID NO:3" has been added after the amino acid sequence KLVFFAE.

In Claim 21, "inclusion" has been changed to "incorporation."

In Claim 26, "SEQ. ID. NO. 1" has been amended to "SEQ ID NO:1."

Therefore, objection to Claims 1, 8, 16, 17, 21 and 26 is overcome and withdrawal of the objection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112 SECOND PARAPGRAPH:

Claims 1 – 28 and 43 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is respectfully submitted that the rejections have been overcome by the presently submitted amendments.

Claim 1 has been amended to clearly define the embodiments of the present invention. In the amended Claim 1, "a separate peptide-containing molecule" has not been amended, because it clearly refers to "a separate molecule that contains a peptide." In addition, "at least one of which is an Nα-substituted α-L-amino-acid residue" has been changed to "at least one of which is Nα-substituted with an Nα-substitutent." Furthermore, "any two successive Nα-substituted α-L-amino-acid residues" has been changed to "any successive Nα-substituted α-L-amino acid

residues." It is clear that in the phrases "all of which ..." and "at least one of which ...", "which" is referring to the "at least four consecutive α-L-amino acid residues".

Claim 4 has been amended such that the Nα-substituent hinders association of the second edge of the β-strand with any other β-strand, whether this other β-strand forms part of a separate peptide-containing molecule or part of the same molecule. This clarifies that the said association may be either intermolecular *or* intramolecular. The fact that the Nα-substituent is sterically hindering association of the said second edge makes it irrelevant whether it is hindering intermolecular or intramolecular association. It is simply inhibiting any association of the second edge with another β-strand. In addition, the antecedent basis for "the Nα-substituent" has been provided in Claim 1.

Claim 6 has been amended to clarify that the term "it" refers to "said group", not subgroup.

Regarding Claim 12, it is respectfully submitted that the term "extends beyond" is clearly defined on page 29, lines 20-30 of the specification of the present application as filed. This term is clear to a person skilled in the relevant art, who is aware of the problem of β-sheets stacking.

In Claim 15, "glycine" has been deleted following the Examiner's suggestion.

Regarding Claim 18, it is respectfully submitted that "mimic thereof" is defined on page 9, line 25 to page 10, line 6 of the specification of the application as filed. This is the terminology regularly used in the field of peptide chemistry and would be clear and accepted by a person skilled in the art. A "peptide mimetic" is, by definition, a "non-peptide compound", but may also be a hybrid structure comprising peptide as well as non-peptide elements, for example, if only one or some of the backbone peptide groups in a peptide are replaced by other chemical groups of similar stereochemistry and ability to form favorable non-covalent interactions with a target β-strand.

Regarding Claim 19, it is respectfully submitted that, as clearly described on pages 31-32 of the present application, a membrane-penetrating section of peptide may be attached to the β-strand-forming section of peptide either directly or indirectly, for example "by including it in the solid-phase synthesis of the β-strand-forming section of peptide as one continuous peptide" or "via an amide or disulphide bond to one of the side chains". Therefore, Applicant respectfully submitted that it would be clear to a person skilled in the art that the membrane-penetrating section of peptide may be attached to the β-strand-forming section of peptide either directly or

indirectly, by any means commonly known to one skilled in the field of peptide chemistry. In addition, the phrase "biological barriers such as cell membranes and the blood-brain barrier" has been amended to "cell membranes, the blood-brain barrier or any other biological barrier". This clarifies the intended scope of the claim 19. The same change has been made to the same phrase ("biological barriers such as cell membranes and the blood-brain barrier") in Claim 24.

In Claim 20, the term "and a side chain of ... or arginine" has been changed to "and the side chains of ... and arginine", in order to provide the required Markush language.

Regarding Claim 22, it is respectfully submitted that the term "forms part of a larger peptide" as described in lines 4 to 9 of page 32 the specification of the present application, would be clear to a person skilled in the art. The size of the peptide is irrelevant. It is discussed on page 33, for example, that it could be a functional component, which works in tandem with the β-strand-forming section.

Regarding Claim 23, it is respectfully submitted that the term "functional component" in claim 23 would be clear to a person skilled in the art as meaning "any atom or group that provides any additional functionality to the chemical compound or composition as a whole" as clearly described by the wide range of specific examples provided on page 33 of the specification of the present application.

In Claim 25, proper amendment has been made to clarify the attachment of the β-strand forming section of the peptide to the functional components.

Regarding Claim 27, it is respectfully submitted that the term "backbone peptide groups" is described clearly from line 21 on page 9 to line 5 on page 10 of the specification of the present application as filed, and would be clear to a person skilled in the art as meaning CONH, if the backbone peptide group is not Nα-substituted, or CON(R), if the backbone peptide group is Nα-substituted.

In Claim 28, proper amendment has been made to clarify the alternative peptide backbone substitutions as described from line 21 on page 9 to line 5 on page 10 of the specification of the present application as filed.

Therefore, the rejection under 35 U.S.C. § 112, second paragraph, has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 102:

Claims 1, 4 – 13, 15, 22 – 24 and 26 have been rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Quibell M. et al. (J. Chem. Soc. Perkin. Trans (1995)1, 2019-2024), hereinafter Quibell.

Applicant traverses the rejection and respectfully submits that the present-claimed invention is not anticipated by the cited reference. As indicated above, the amended Claim 1 further clarifies the scope of the embodiments of the present invention. More specifically, the amended Claim 1 defines "[A] chemical compound or composition comprising a peptide, said peptide comprising a β-strand-forming section of peptide, wherein:

(a) said β-strand-forming section of peptide comprises a peptide backbone and forms a β-strand having two edges, a first edge and a second edge, corresponding to opposite sides of said peptide backbone;
(b) said first edge associates with a target β-strand formed by a separate peptide-containing molecule;
(c) said β-strand forming section of peptide comprises a sequence of at least four consecutive α-L-amino acid residues, all of which have side chains able to form favorable non-covalent interactions with neighboring side chains of the target β-strand, and at least one of which is Nα-substituted with an Nα-substituent, and
(d) any successive Nα-substituted α-L-amino acid residues are separated by an odd number of consecutive Nα-unsubstituted α-L-amino acid residues, such that the Nα-substituent(s) lie along only said second edge."

Claims 4 – 13, 15, 22 – 24 and 26 also include these features due to their dependency on Claim 1. Especially, Claim 1 clearly defined that "said β-strand-forming section of peptide comprises a peptide backbone and forms a β-strand having two edges, a first edge and a second edge, corresponding to opposite sides of said peptide backbone." Therefore, it is clear that the "edge" is not N- or C-terminal region of compounds disclosed in Quibell as alleged. Applicant respectfully submits that it is incorrect to refer to the N-terminal region (residue 1 to 22) of the peptide disclosed in Quibell as being equivalent to "the first edge of the instant application" and the C-terminal region (residue 25 – 43) of the peptide disclosed in Quibell as being equivalent to "the second edge β-strand-forming section of the instant application."

In addition, the embodiment of the present invention includes one edge of a β-strand-forming section of peptide "associating with a target β-strand formed by a separate peptide-containing molecule". As described from line 33 on page 15 of the present application, these two β-strands "associate in either the parallel or antiparallel orientation ... by means of hydrogen bonds between their backbone peptide groups and additional non-covalent interactions between their side chains". Therefore, if a particular β-strand-forming section of peptide is unable to associate with a target β-strand in this way when it forms only part of a longer peptide, in the context of the chemical compound or composition as a whole, it cannot be considered to be a "β-strand-forming section of peptide" according to claim 1.

The present invention provides peptides comprising a "β-strand-forming section of peptide" (referred to herein as the "Core Section"), which forms β-strand, wherein at least one amino acid of the said section is Nα-substituted with an Nα-substituent ("Blocking Group"). The compounds of the present invention as claimed are formed by relying on the use of Blocking Groups along one edge (or side) of the Core Section to inhibit association along only that one edge, while allowing association along the other edge. The Core Section must maintain these functional characteristics *in situ*, i.e., when forming part of a larger peptide within the compound or composition as a whole. The features of these compounds are shown in Figures 1 & 2 below.

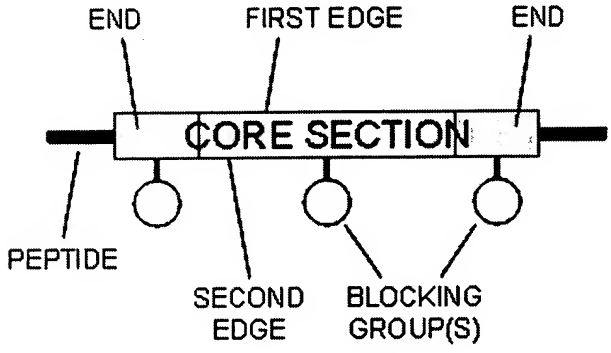
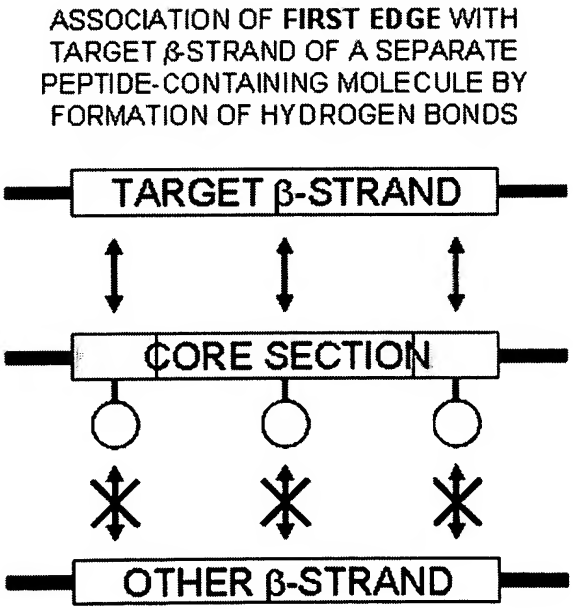


Figure 1

Figure 2 →



It would be appreciated that the term "edge" used throughout the claims of the present invention refers to each side of the Core Section. It is well known to people skilled in the art that formation of β-sheets results from the association of β-strands, arranged side-by-side, by the formation of hydrogen bond interactions between the edges of their peptide backbones. This is explained very clearly from line 23 on page 7 to line 9 on page 8 of the present application. The aim of the compounds of the present invention is to prevent the formation of extended β-sheets, by allowing the association of only one (first) edge of the Core Section with a target β-strand, while inhibiting association of the other (second) edge of the Core Section with any other β-strand.

The Disclosure in Quibell

It is respectfully submitted that the disclosure in Quibell is different from the embodiment of the present invention as amended. Applicant respectfully submits that the Examiner has misinterpreted the term "edge" to be the ends of a peptide chain. When considering the peptide disclosed on page 2020 of Quibell, the Examiner refers to the N-terminal region (residues 1 to 22) of the peptide as being "equivalent to the first edge of the instant application" and the C-terminal region (residues 25-43) of the peptide as being "equivalent to the second edge β-strand-forming section of the instant application". The above interpretation is incorrect under the claims as amended. "The edges" are along the sides of the formed β-strand, rather than "the ends" as disclosed in Quibell. To assist the Examiner in understanding the embodiments of the present invention, Applicant enclosed herewith a paper by the inventor – Meptides: a potential treatment for neurodegenerative diseases – which explains how the claimed compounds/compositions function.

The Nα-substituted peptides described by Quibell were specifically designed and prepared as synthetic intermediates, to circumvent aggregation of the native, Nα-unsubstituted β-amyloid(1-43) peptide during its synthesis (see abstract and bottom of column 1 on page 2019). De-*O*-acetylation and cleavage/removal of the AcHmb backbone-protecting groups to produce the final unsubstituted peptide is described in the last two sections (6 and 7) on page 2023. On

page 2019 (see paragraph 2 of column 2), Quibell reports the "unexpected aggregation" of their (Hmb)Gly38-substituted β-amyloid(1-43) peptide (sequence shown at the top of page 2020) during its synthesis from the C-terminus, which was observed as "a moderately broadened Fmoc-deprotection profile at Met35", having added only the first 9 residues comprising the C-terminal segment of the peptide (residues 35 to 43). The authors claim that this, to their knowledge, "is the first example in which Hmb incorporation has not provided complete inhibition of aggregation" and they concluded that "this unexpected aggregation could not be due to the formation of simple intermolecular β-sheet structures composed of fully extended peptide chains", because this would be prevented by the presence of the Nα-substituted (Hmb)Gly38 residue. The reason for this unexpected aggregation was studied and is explained in paragraph 3, column 2 on page 2019, and in Figures 1(a) and 1(b) on page 2021. This is shown in Figures 1(a) and 1(b) in the Quibell (reproduced below as Fig. 3).

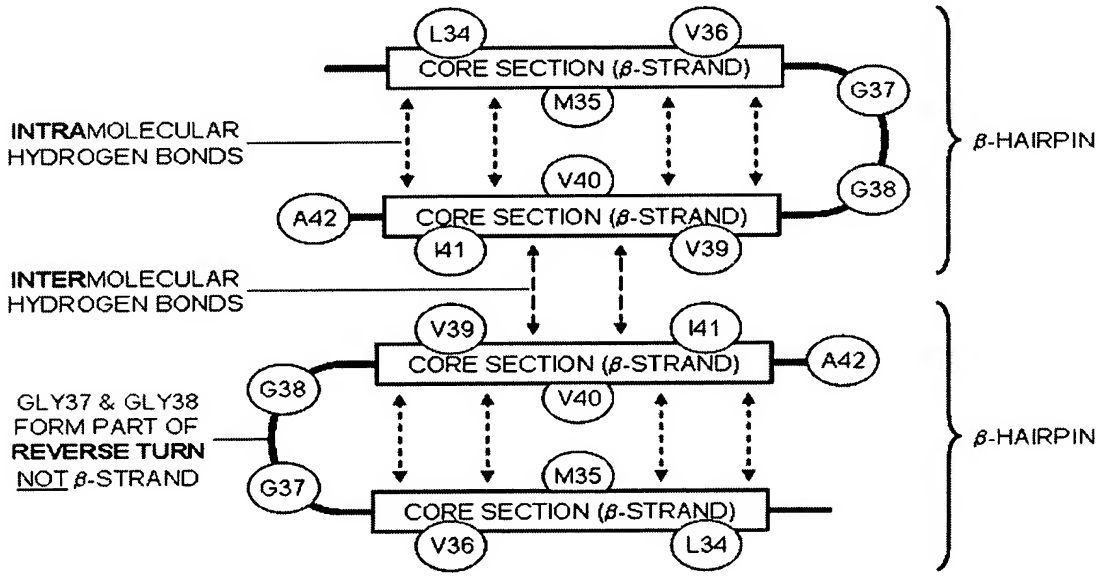


Figure 3

A "detailed investigation" revealed that the C-terminal segment (residues 34-42) of the peptide forms a stable β-hairpin structure, which "consists of a reverse turn (residues Val36 to Val39), connecting two β-strands (residues Leu34 to Val36 and Val39 to Ile41, respectively) so as to form an antiparallel, intramolecular β-ribbon", as shown in Figure 1(a). The paper explains that "these stable β-hairpin structures could themselves associate to form all-β polymers, by lateral, intermolecular pairing of self-similar β-strands", as shown in Figure 1(b). The use of the term "β-strand" in the Quibell paper is completely consistent with the definition used throughout the

present application, as described on page 7, starting at line 23. This makes a direct comparison of the molecules disclosed in Quibell and those covered by the present invention, relatively straightforward.

Figure 1(b) on page 2021 clearly shows that the unexpected aggregation of the peptide molecules occurs by the intermolecular association of two β-strands comprising residues Leu34 to Val36 and Val39 to Ile41, respectively. Moreover, Quibell has gone to great lengths to reveal that the peptide molecules aggregate in this way (i.e., by the association of these two particular β-strands), since they concluded that the "unexpected aggregation could not be due to the formation of simple intermolecular β-sheet structures composed of fully extended peptide chains" – no other β-strand-forming sections are identified within the peptide studied by Quibell, and no other sections of the peptide are involved in its intermolecular association/aggregation.

The key point here is that neither of the two β-strands identified by Quibell comprise an Nα-substituted α-L-amino-acid residue, as indicated in the amended claims of the present invention. The only residues which have been modified in this region (residues 34-42) are Gly37 and Gly38, however both these residues reside in the reverse turn (residues Val36 to Val39) of the β-hairpin structure (see paragraph 3, column 2 on page 2019, and Figures 1(a) on page 2021), rather than in either of its two β-strands as indicated in the amended claims of the present invention.

Although it may be possible to select other sections of the Quibell molecule which comprise "at least four consecutive α-L-amino-acid residues ... at least one of which is Nα-substituted with an Nα-substituent", no such sections would be capable of associating "with a target β-strand formed by a separate peptide-containing molecule" as indicated in the amended claims of the present invention. This is because the Nα-Hmb substituents have been positioned (by design) to lie on both odd and even residues throughout the peptide, in order to prevent any such intermolecular association. Moreover, Quibell showed that the "unexpected aggregation" occurs by association of the two β-strands comprising residues Leu34 to Val36 and Val39 to Ile41, respectively – no other sections of the peptide are involved in this intermolecular association/aggregation; and no other β-strand-forming sections of the peptide are identified by

Quibell. Therefore, any other section of the Quibell peptide which could be selected arbitrarily cannot be a "β-strand-forming section of peptide having ... a first edge which associates with a target β-strand formed by a separate peptide-containing molecule" as defined by the present invention.

Therefore, the Quibell reference does not disclose a "chemical compound or composition comprising a peptide, which peptide comprises a β-strand-forming section of peptide ... comprising a peptide backbone and forming a β-strand having two edges, a first edge and a second edge, ... , said first edge associates with a target β-strand formed by a separate peptide-containing molecule, ... wherein the β-strand-forming section of peptide comprises a sequence of at least four α-L-amino-acid residues, ... at least one of which is Nα-substituted with an Nα-substituent", as indicated in the embodiment of the present invention as claimed.

Therefore, the newly presented claim is not anticipated by Quibell and the rejection under 35 U.S.C. § 102 (b) has been overcome. Accordingly, withdrawal of the rejection under 35 U.S.C. § 102 (b) is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §101:

Claims 1 – 4, 6 – 17, 19, 20, 22 – 28 and 43 have been provisionally rejected under 35 U.S.C. §101 as allegedly claiming the same invention as Claims 1 – 4, 5 – 22, 24 – 26 and 41 of U.S. Application No. 10/030,138 (hereinafter '138 application), respectively.

Applicant traverses the rejection and respectfully submits that the embodiments of present-claimed invention are different from the subject matter of '138 application. It is respectively submitted that the compounds of the present application comprise β-strand-forming sections of α-L-amino acid residues. By contrast, the compounds of '138 application comprise β-strand-forming sections of α-D-amino acid residues. The claims of these two applications are therefore mutually exclusive because they relate to two different (L or D) enantiomeric forms of amino acid residues, which are chemically distinct from each other. It should also be appreciated by the Examiner that peptides comprising one or other of these two enantiomers have very

different chemical characteristics. In fact, some of the key differences are described in lines 7 to 14 on page 10 and in lines 12 to 27 on page 17 of the present application:

(i) L-amino acids occur more commonly in nature and are therefore cheaper than D-amino acids, which usually have to be made synthetically; and

(ii) L-amino acids are more susceptible than D-amino acids to proteolysis, if left unprotected.

Furthermore, it has been found that the efficacy of peptides comprising α-L- and α-D-amino acid residues as amyloid aggregation inhibitors differs greatly between the two enantiomers, as shown in the accompanying paper by Chalifour *et al.*

Therefore, the rejection under 35 U.S.C. §103, second paragraph, has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. §103 is respectfully requested.

Having overcome all outstanding grounds of rejection, the application is now in condition for allowance, and prompt action toward that end is respectfully solicited.

Respectfully submitted,

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Enclosures:

1. Copy of A Paper Entitled - Meptides: a potential treatment for neurodegenerative Diseases;
2. Copy of A Paper by Chalifour *et al.* Entitled – Stereoselective Interactions of Peptide Inhibitors with the β-Amyloid Peptide.